

# PATENT SPECIFICATION

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## (54) ANALGETIC COMPOSITION

(71) We, BRISTOL-MYERS COMPANY, a Corporation organized and existing under the Laws of the State of New York, United States of America, of 345 Park Avenue, New York, State of New York, 10022, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:

This invention relates to an analgetic composition containing naloxone.

Drug abuse has almost become a way of life to a rapidly growing segment of the world population, especially in the United States. It has become the vogue of many of the younger generation to experiment with any type of drug that will produce an emotional, psychological, euphoric, depressive or generally psychotropic experience.

Those drugs most commonly employed for such illicit purposes include the barbiturates, lysergic acid diethylamide (LSD), mescaline, marijuana (*tetrahydrocannabinol*), strong analgetics (e.g. heroin, codeine, morphine, meperidine, propoxyphene [Darvon] methadone, dihydromorphone and pentazocine, the central nervous system stimulants (e.g. the amphetamines) and some of the major and minor tranquilizers (e.g. the promazines, propantheline, imipramine and the diazepines). Most of these compounds are commonly used in medicine for the legitimate treatment of various conditions and therefore have a limited availability in our society. While these agents are a necessary part of modern medicine, it would be highly desirable either 1) to produce new drugs that do not possess drug abuse potential or 2) to "denature" the old agents to prevent their illicit use. The pharmaceutical industry has been striving to achieve the first goal for many years but most regrettably has only achieved very moderate success. If one focuses on the strong analgetics, it becomes apparent that much effort and money has been expended to produce chemicals possessing good analgetic activity but little or no addictive

liability. While good progress has been made as evidence, for example, by the development of propoxyphene as a replacement for codeine and pentazocine as a replacement for morphine and meperidine, it is unfortunate that these compounds are still reported in the medical literature to be addictive and/or euphoric and subjected to abuse by parenteral administration. Furthermore, some of these agents have undesirable side effects, e.g. bad hallucinations.

It is commonly known to the narcotic enforcement agencies and others in the medical trades that substantially large amount of the strong analgetics destined for legitimate medicinal use become diverted by dishonest or careless handling. In most instances these compounds are obtained by the addict or potential addict by theft or casual prescribing practice by the physician.

It is known from experience that the true narcotic addict, must feed his habit by the parenteral route (mainlining) to obtain the maximum euphoric effect. The potential addict or thrill-seeker will also experiment in the same manner. Unfortunately, a substantial amount of the legitimate strong analgetics formulated in oral dosage form are diverted to parenteral use and abuse. Since the oral dosage forms of these drugs diverted from legitimate channels must be parenterally usable to produce the desired euphoria, it follows that if these oral dosage forms are in some way rendered inactive or unpleasant for parenteral use of addict or potential addict will be cut off from this particular supply of euphoric drugs.

Naloxone, chemically known as 1 - N - allyl - 1,4 - hydroxynordihydromorphone (Merck Index, 8th Ed., p. 712, Merck & Co., Rahway, New Jersey, U.S.A. Patent No. 3,294,088 [1966]), is a potent narcotic antagonist when administered parenterally and as such is useful for the treatment or narcotic overdose or for the detector of addiction. However, while naloxone is extremely potent parenterally (a parenteral dose of 0.1 mg. to 2.5 mg. will produce narcotic withdrawal symptoms in the addict or have a narcotic

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reversal effect in an overdose situation), the compound must be administered in quantities 200 to 400 times greater than the parenteral dose to obtain the same effect orally. It is known that the contemporaneous parenteral administration of equivalent therapeutic doses of naloxone and an euphoric narcotic or narcotic-like analgesic will negate the analgesic and euphoric effect in the normal individual and the euphoric and/or maintenance effect of the analgesic in the addict.

Many interchangeable terms are commonly used to describe the psychic or physical dependence of people upon drugs. The term 15 addition is most commonly used when talking about the strong analgesics. The strong analgesics, in contrast to the weaker agents such as aspirin and acetaminophen are employed in the relief of more severe pain.

They usually produce a euphoric effect on 20 parenteral administration.

Addiction can develop to barbiturates and strong analgesic agents, in the sense of the term "addictive" as defined by the Committee 25 on Problems of Drug Dependence of The National Research Council, formerly known as the Drug Addictives Committee of The National Research Council, namely, a state of periodic or chronic intoxication detrimental to the individual and to society, produced by the repeated administration of a drug, its characteristics are a compulsion to take the drug and to increase the dose, with the development of psychic and sometimes physical dependence 30 on the effects of the drug, so that the development of means to continue the administration of the drug becomes an important motive in the addict's existence.

Addiction to the strong narcotic or narcotic-like analgesics often occurs by the legitimate chronic parenteral administration of these agents in the alleviation of deep pain. More commonly, however, addiction to these agents occurs when the psychologically unbalanced or thrill-seeking individual looking for an escape from the realities of life finds his escape in the euphoria produced by the parenteral administration of strong analgesics. Euphoria is generally defined as a feeling of well-being. 45 Euphoria can be produced in many ways, e.g., through an exhilarating experience or the use of alcohol, stimulants, depressants and narcotics. For the purpose of this specification, "euphoria" is defined as an abnormal state of well-being produced by the parenteral administration of strong analgesic agents.

We have now found that by using a combination of naloxone and an analgesic agent there can be produced a potent, orally effective, but parenterally inactive analgesic composition that has essentially no drug abuse potential, i.e. a composition which has the effect of preventing the analgesia, euphoria and/or physical dependence resulting when an orally active strong analgesic agent intended

for oral administration is abused by parenteral administration.

Accordingly, the present invention provides an analgesic composition in oral dosage form, which composition comprises an orally active strong analgesic agent and an amount of naloxone sufficient to negate the analgesic and/or euphoric action of the composition upon parenteral administration but insufficient to negate the analgesic and/or euphoric action of the composition upon oral administration.

By the term "strong analgesic agent" (or "euphoric analgesic") as used herein is meant a narcotic or narcotic-like analgesic which upon parenteral administration is capable of maintaining or partially maintaining a person addicted to an addictive analgesic such as heroin without substantial withdrawal symptoms.

By combining a parenterally effective but orally ineffective dose of naloxone with an oral analgesic dose of an orally effective strong analgesic it is possible to avoid interference with the analgesic effect of the analgesic upon oral administration while, at the same time, if any of the oral dosage form should be diverted into the hands of the addict or potential addict, the composition when injected parenterally would not produce any analgesia, euphoria and/or physical dependence, and, in an addict would, in fact, actually cause some withdrawal symptoms.

Examples of some representative orally active strong analgesics and their preferred oral dosage ranges are: meperidine (50—250 mg.), 100 oxymorphone (5—25 mg.), alphaprodine (50—250 mg.), amleridine (25—150 mg.), dextromethoramide (5—25 mg.), dextropropoxyphene (32—150 mg.), methadone (5—25 mg.), metopon (5—15 mg.), levorphanol (2—10 mg.), phenazocine (2—10 mg.), ethephenazine (100—500 mg.), propifum (50—500 mg.), profadol (20—250 mg.), phenansprromide (30—250 mg.), thiambutene (20—150 mg.), penazocine (20—200 mg.), pholedocine (25—250 mg.), codeine (15—150 mg.), oxycodeone (5—50 mg.), dihydrocodeine (5—100 mg.), hydromorphone (10—100 mg.), fentanyl (0.5—10 mg.), 3 - trans - dimethylamine - 4 - phenyl - 4 - trans - carbethoxy -  $\Delta'$  - cyclohexene (50—250 mg.), 3 - dimethylamino - O - (4 - methoxyphenylcarbamoyl) - propiophenone oxime (25—150 mg.), (-)-2' - hydroxy - 2,9 - dimethyl - 5 - phenyl - 6,7 - benzomorphan (10—150 mg.), (-)2' - hydroxy - 2 - (3 - methyl - 2 - butenyl) - 9 - methyl - 5 - phenyl 6,7 - benzomorphan (20—300 mg.) piritramide (10—150 mg.), (-)2 - 5,9 - diethyl - 2' - hydroxy - 2 - methyl - 6,7 - benzomorphan (50—250 mg.), ethyl 1 - (2 - dimethylaminomethyl) - 4,5,6,7 - tetrahydro - 3 - methyl - 4 - oxo - 6 - phenylindole - 2 - carboxylate (50—150 mg.), 1 - (m - benzoylmethyl) - 2,3 - dimethyl - 3 - (m - hydroxyphenyl) - piperidine (50—500 mg.)

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- mg.), N - allyl - 7 $\alpha$  - (1 - (R) - hydroxy - 1 - methylbutyl) - 6,14 - endo - ethenotetrahydronorpavine (50 - 250 mg.), (-) $\gamma$ ' - hydroxy - 2 - methyl - 6,7 - benzomorphan (50 - 250 mg.), noracetylmethadol (10 - 150 mg.) phenoperidine (5 - 100 mg.),  $\alpha$  - dl - methadol (5 - 25 mg.),  $\beta$  - dl - methadol (35 - 250 mg.),  $\alpha$  - 1 - methadol (2 - 15 mg.),  $\beta$  - dl - acetylmethadol (1 - 10 mg.),  $\alpha$  - 1 - acetylmethadol (1 - 10 mg.) and  $\beta$  - 1 - acetylmethadol (2 - 25 mg.).
- When the term naloxone or the name of a strong analgesic agent is used herein, it is to be understood that any and all the pharmaceutically acceptable nonionic salts thereof are embraced by the term. Such salts include, amongst others, the hydrochlorides, sulfates, bisulfates, tartrates, nitrates, citrates, bitartrates, phosphates, malates, maleates, 15 hydrobromides, hydroiodides, fumarates, malates, maleates, hydrobromides, hydroiodides, fumarates, and succinates.
- The compositions of the present invention are made by mixing an orally ineffective but 20 parenterally effective dose of naloxone with an orally active strong analgesic. The naloxone and strong analgesic are preferably combined in amounts of about 0.1 mg. to about 10 mg., and most preferably about 0.1 mg. to about 2.5 mg., of naloxone per analgesic oral dose of the orally active strong analgesic.
- The compositions of the present invention can be formulated into any of the known pharmaceutical forms for oral administration. 25 As such the term "oral dosage form" includes solid compositions for oral administration in unit dosage form such as tablets, capsules, granules, powders, and cachets. Bulk powders of fixed composition for subdivision into therapeutic quantities, solutions, emulsions or suspensions of the composition are also included in the definition.
- The compositions of the present invention can also contain other active ingredients. These 30 include amongst others, for example, aspirin, phenacetin, caffeine, acetaminophen, anti-histamines, homatropine, methylbromide, phenyltoloxamine citrate, barbiturates; or mixtures thereof. Also included within the scope of the present invention are those compositions comprising naloxone in combination with those antidiarrheal preparations which contain narcotic or narcotic-like cough suppressants such as codeine, dihydrocodeine, 35 and phocodine. In addition other products comprising a narcotic or narcotic-like composition for use as an antispasmodic in the gastro-intestinal tract, such as Camphorated Optium Tincture, U.S.P., Optimum Tincture, U.S.P. and Optimum Extract, N.F. can be denatured with naloxone and they too are considered within the scope of this invention.
- The weight ratios of naloxone to the analgesic agents in the compositions of the present invention have been determined either from the literature or in our laboratories. It has been found that the parenteral administration of one part by weight of naloxone will efficiently and reliably negate (counteract) the parenteral effect of up to about 400 parts of meperidine, 4 parts of oxymorphone, 150 parts of alphaprodine, 120 parts of eniferidine, 20 parts of dextromoramide, 120 parts of dextropropoxyphene, 25 parts of methadone, 3 parts of metopon, 8 parts of levorphanol, 8 parts of phenazocine, 600 parts of etheptazine, 200 parts of propranol, 80 parts of profadol, 400 parts of phenampromide, 100 parts of thiambutene, 80 parts of pentazocine, 40 parts of phocodine, 150 parts of codeine, 20 parts of oxycodone, 25 parts of dihydrocodeine, 8 parts of hydromorphone, 1 part of fentanyl, 150 parts of 3 - trans - dimethylamino - 4 - phenyl - 4 - trans - carbethoxy - 4' - cyclohexene, 60 parts of 3 - dimethylamino - O - (4 - methoxybenzylcarbamoyl) - propiophenone oxime, 50 parts of (-) $\beta$  - 2' - hydroxy - 2,9 - dimethyl - 5 - phenyl - 6,7 - benzomorphan, 130 parts of (-) $\gamma$ ' - hydroxy - 2 - (3 - methyl - 2 - butenyl) - 9 - methyl - 5 - phenyl - 6,7 - benzomorphan, 50 parts of piritramide, 50 parts of ethyl 1 - (2 - dimethylaminoethyl) - 4,5,6,7 - tetrahydro - 3 - methyl - 4 - exo - 6 - phenylindole - 2 - carbonylate, 200 parts of 1 - benzylmethyl - 2,3 - dimethyl - 3 - (m - hydroxyphenyl) - piperidine, 1 - part N - allyl - 7 $\alpha$  - (1 - (R) - hydroxy - 1 - methylbutyl) - 6,14 - endo - etheno - tetrahydronorpavine, 140 parts of (-) $\gamma$ ' - hydroxy - 2 - methyl - 6,7 - benzomorphan, 50 parts of noracetylmethadol, 20 parts of phenoperidine, 25 parts of  $\alpha$  - dl - methadol, 400 parts of  $\beta$  - dl - methadol, 3 parts of  $\alpha$  - 1 - methadol, 8 parts of  $\beta$  - dl - acetylmethadol, 8 parts of  $\alpha$  - 1 - acetylmethadol and 4 parts of  $\beta$  - 1 - acetylmethadol.
- Thus in a preferred embodiment the composition of the invention comprises by weight one part of naloxone per 40 to 400 parts of meperidine, 0.4 to 4 parts of oxymorphone, 13 to 130 parts of alphaprodine, 12 to 120 parts of eniferidine, 2 to 20 parts of dextropropoxyphene, 2.5 to 25 parts of methadone, 0.3 to 3 parts of metopon, 0.8 to 8 parts of levorphanol, 0.8 to 8 parts of phenazocine, 60 to 600 parts of etheptazine, 20 to 200 parts of propranol, 8 to 80 parts of profadol, 40 to 400 parts of phenampromide, 10 to 100 parts of thiambutene, 8 to 80 parts of pentazocine, 4 to 40 parts of phocodine, 15 to 150 parts of codeine, 2 to 20 parts of oxycodone, 2.5 to 25 parts of dihydrocodeine, 0.8 to 8 parts of hydromorphone, 0.1 to 1 parts fentanyl, 15 to 150 parts 3 - trans - dimethylamino - 4 - phenyl - 4 - trans - carbethoxy - 4' - cyclohexene, 6 to 60 parts of 3 - dimethylamino - O - (4 - methoxy-

- phenyl - carbamoyl) - propiophenone oxime, 5 to 50 parts of  $(-\beta - 2'$  - hydroxy - 2,9 - dimethyl - 5 - phenyl - 6,7 - benzomorphan, 13 to 130 parts of  $(-\gamma' 2'$  - hydroxy - 2 - (3 - methyl - 2 - butenyl) - 9 - methyl - 5 - phenyl - 6,7 - benzomorphan, 5 to 50 parts of pirinutramide, 5 to 50 parts of  $(-\alpha 2$  - 5,9 - diethyl - 2' - hydroxy - 2 - methyl - 6,7 - benzomorphan, 5 to 50 parts of ethyl 10 1 - (2 - dimethylaminooethyl) - 4,5,6,7 - tetrahydro - 3 - methyl - 4 - oxo - 6 - phenylindole - 2 - carboxylate, 20 to 200 parts of 1 - Benzoylmethyl - 2,3 - dimethyl - 3 - (n - 15 hydroxymethyl) - pipericidine, 0.1 to 1 parts of N - allyl - 7a - (1 (R) - hydroxy - 1 - methylbutyl) - 6,14 - endo - ethenosteratetrahydrocortexazine, 14 to 140 parts of  $(-\gamma' 2'$  - hydroxy - 2 - methyl - 6,7 - benzomorphan, 5 to 50 parts of noracetylmethadol, 2 to 20 parts of phenoperidine, 2.5 to 25 parts of  $\alpha$  - dl - methadol, 40 to 400 parts of  $\beta$  - dl - methadol, 0.3 to 3 parts of  $\alpha$  - 1 - methadol, 0.8 to 8 parts of  $\beta$  - dl - acetyl - methadol, 0.8 to 8 parts of  $\alpha$  - 1 - acetylmethadol or 0.4 to 4 20 parts of  $\beta$  - acetylmethadol.
- It has also been established that naloxone can be administered orally in a quantity up to about ten times the minimal parenteral dose required to abolish parenteral activity of the analgesic without abolishing the oral activity of the analgesic, e.g. 1 part naloxone per 40 parts merperidine or 1 part naloxone per 0.8 parts phenazocine.
- Working from these parenteral ratios which define the minimum efficient and reliable parenteral dose of naloxone required to negate the parenteral dose of the analgesic agent, other experiments have been conducted to determine the largest practical and contemplated quantity of naloxone that can be administered orally per oral therapeutic dose of the analgesic agent without abolishing the oral effect of the analgesic agent. It was found that the one can safely administer naloxone orally in a quantity up to about 10 times the minimal parenteral dose necessary to abolish parenteral activity of the orally effective dose of the analgesic. It is emphasized here that it is frequently possible to orally administer more than 10 times the minimum parenteral dose of the naloxone without abolishing the oral analgesic effect.
- The "rat tail-flick" method was used in our laboratory to determine the naloxone analgesic ratios of some of the euphoric analgesic agents. The method adopted for use is that originally described by D'Amour and Smith (J. Pharmacol. Exper. Therap. 72:74, 1941) in which a heat lamp is focused onto a rat's tail and the elapsed time between onset of the light and a flick of the tail is measured. The method consists of holding the animal either by wrapping it in a towel or box with the tail laying in a V-shaped groove. The 40 light and timer are connected in series with a switch so that both the light and timer can be turned on and off simultaneously. When the rat quietes down, the light and timer are turned on and the operator watches for the response, which is a characteristic flick of the tail. The response, in the control period for the untreated rat is usually about 3.5 seconds. Rats weighing between 160 to 190 grams have been found most uniform in response in the control and treated trials.
- An example of one experiment is the determination of the parenteral ratio for oxy-morphine in rats.
- Untreated rats produced the desired "tail-flick" in 3.5 seconds. A differing amount of oxy-morphine hydrochloride was administered subcutaneously to a sequence of rats to determine the minimum quantity of oxy-morphine hydrochloride necessary to delay the "tail-flick" till 7 seconds. The amount required was 0.22 mg./kg. body weight.
- A series of rats so treated with oxy-morphine hydrochloride were then challenged with varying doses of subcutaneously administered naloxone hydrochloride to determine the minimum quantity of naloxone that would completely negate the analgesia produced by the oxy-morphine. The quantity required was 0.025 mg./kg. body weight. The parenteral naloxone/analgesic ratio is therefore approximately 1 part naloxone hydrochloride to about 9 parts of oxy-morphine hydrochloride.
- Once it was established that the parenteral administration of 1 part of naloxone would completely negate the analgesic activity of about 9 parts of oxy-morphines, it was necessary to determine how the ratio would work when the combination was administered orally.
- A series of starved rats were orally dosed by stomach tube with varying quantities of oxy-morphine to determine the oral dose of oxy-morphine necessary to produce a "tail-flick" response of 7 seconds. The dose of oxy-morphine hydrochloride was dissolved in 20 ml. of water per kg. of body weight. It was determined that 50 mg./kg. orally produced the desired "tail-flick" response in 6 of 6 rats. A dose of 25 mg./kg. produced the desired response in 5 of 6 rats.
- A composition of 1.1 grams of naloxone hydrochloride and oxy-morphine hydrochloride was prepared containing 0.1 gram of naloxone HCl and 1.0 gram of oxy-morphine HCl (1:10 ratio).
- A dose of 27.5 mg./kg. of body weight of the above composition dissolved in 20 ml. of water was administered by stomach tube. Six of 6 rats showed a "tail-flick" response of at least 7 seconds. When a dose of 55 mg./kg. was administered, 6 of 6 rats again showed the desired analgesic effect of at least 7 seconds.
- In a similar experiment to that described above, it was determined that 50 mg./kg. of 130

- phenazocine orally produced the desired "tail-flick" response in 5 of 6 rats. A dose of 100 mg./kg. produced the desired response in 6 of 6 rats.
- 5 A composition of 0.64 gm. of naloxone hydrochloride and phenazocine hydrobromide was prepared containing 0.04 gm. of naloxone HCl and 0.60 gm. of phenazocine HBr (1:15 ratio).
- 10 A dose of 53.3 mg./kg. of body weight of the above composition dissolved in 20 ml. of water was administered by stomach tube. Six of 6 rats showed a "tail-flick" response of at least 7 seconds. When a dose of 106.6 mg./kg. was administered, 6 of 6 rats again showed the desired analgesic effect of at least 7 seconds.
- In further experiments with phenazocine HBr, it was found that compositions containing doses of naloxone in 100% excess of the 20 minimal antagonistic parenteral dose still produced analgesia upon oral administration.
- The conclusion can therefore be drawn that a parenterally antagonistic dose of naloxone can be administered orally without interfering with the analgesic effect of the orally administered analgesic.
- Applicants acknowledge the possibility of different naloxone/analgesic ratios due to species differences, e.g., rat versus man. For 30 example, our laboratory studies show a part or parenterally administered naloxone hydrochloride will negate the analgesic effect of about 9 parts of parenterally administered oxymorphone hydrochloride in the rat. However, it is reported in the literature that 1 part of naloxone HCl parenterally is required to negate the analgesic effect of 4 parts of oxymorphone HCl parenterally in man.
- Likewise, it was found that 1 part of 40 naloxone parenterally could negate the effect of about 15 parts of phenazocine HBr in the rat, but the literature reports that 1 part of naloxone parenterally is required to negate the effect of 8 parts of phenazocine HBr parenterally in man.
- Particularly preferred embodiments of the invention are compositions in unit dosage form which comprise:
- 1 mg. of naloxone to about 2 to about 8 50 mg. of phenazocine.
- 1 mg. of naloxone to about 5 to about 10 mg. of methadone.
- 55 5 mg. of naloxone to about 25 to about 50 mg. of methadone.
- 1 mg. of naloxone to about 30 to about 65 mg. of dextropropoxyphene.
- 1 mg. of naloxone to about 2 to about 8 mg. of levorphanol.
- 1 mg. of naloxone to about 10 to about 60 40 mg. of profadol.
- 1 mg. of naloxone to about 5 to about 25 mg. of (-)-2'-hydroxy-2,9-dimethyl-5-phenyl-6,7-benzomorphan.
- 5 mg. of naloxone to about 5 to about 25 mg. of oxymorphone.
- mg. of (-)-2'-hydroxy-2'-hydroxy-2-methyl-6,7-benzomorphan. 65
- 1 mg. of naloxone to about 10 mg. of oxy-
- morphine.
- One especially valuable composition of the present invention is the orally active combination of methadone and naloxone. This is particularly so because of the recently acknowledged and accepted method of treating former narcotic addicts with methadone. The regimen of treatment involves the oral dosing of the addict one or more times a day with a maintenance dose of methadone adequate to prevent narcotic craving. One major disadvantage of the program is the necessity of the former addict to report to a treatment center one or more times a day to receive his methadone. The oral methadone must be administered in the presence of a health officer to prevent its diversion into illicit channels where it can be abused parenterally so as to obtain a euphoric effect. However, this would not be so if the composition of the present invention were to be employed. As explained above, the naloxone-methadone composition would be orally active but could not be diverted to parenteral use because of the presence of the narcotic antagonist, naloxone. It would therefore be possible to supply an addict with a several days supply of his maintenance dose of methadone without fear of the composition being used in a manner other than that intended.
- The invention includes a method of preventing drug abuse by parenteral administration of an orally active strong analgesic, which method comprises combining the analgesic with naloxone to form a composition in accordance with the invention. 90
- The invention also includes a method of producing analgesia in non-human mammals, which method comprises orally administering to the mammal a composition in accordance with the invention. 100
- The following Examples illustrate compositions in accordance with the invention. 110
- | Example 1               |              |
|-------------------------|--------------|
| Naloxone Hydrochloride  | 0.10 gram    |
| Methadone Hydrochloride | 0.500 gram   |
| Lactose qs. ad.         | 100 capsules |
- | Example 2                |              |
|--------------------------|--------------|
| Naloxone Hydrochloride   | 1.0 gram     |
| Phenazocine Hydrobromide | 2.5 grams    |
| Magnesium Stearate qs.   |              |
| Corn Starch qs. ad.      | 1000 tablets |
- | Example 3                |              |
|--------------------------|--------------|
| Naloxone Hydrochloride   | 0.050 gram   |
| Meperidine Hydrochloride | 5.0 grams    |
| Corn Starch              |              |
| Talc sa qs. ad.          | 100 capsules |

			metopon, levorphanol, phentazocine, etoheptazine, propizam, profadol, phenampromide, thiambutene, pentazocine, phlokodeine, codeine, oxycodone, dihydrocodeine, hydro-morphone, fentanyl, 3 - trans - dimethyl-amino - 4 - phenyl - 4 - trans - carbethoxy - $\Delta^1$ - cyclohexene, 3 - dimethylamino - O - (4 - methoxyphenylcarbamoyl) - propiophenone oxime, ( $-$ ) $\beta$ - 2' - hydroxy - 2,9 - dimethyl - 5 - phenyl - 6,7 - benzomorphan, ( $-$ ) $\alpha$ - 2' - hydroxy - 2 - (3 - methyl - 2 - butenyl) - 9 - methyl - 5 - phenyl-6,7 - benzomorphan, piriminamide, ( $-$ ) $\alpha$ - 5,9 - diethyl - 2' - hydroxy - 2 - methyl - 6,7 - benzomorphan, ethyl 1 - (2 - dimethylaminoethyl) - 4,5,6,7 - tetrahydro - 3 - methyl - 4 - oxo - 6 - phenyl - indole - 2 - carbonylate, 1 - benzoylmethyl - 2,3 - dimethyl - 3 - (m - hydroxyphenyl) - piperidine, N - allyl - 7 $\alpha$ - (R) - hydroxy - 1 - (methylbutyl) - 6,14 - endo - ethenotetrahydronorpavine, ( $-$ ) $\beta$ - 2' - hydroxy - 2 - methyl - 6,7 - benzomorphan, norcynamethadol, norperiperidine, $\alpha$ - di - methyl, $\beta$ - di - methyl, $\alpha$ - 1 - methyl, $\beta$ - di - acetyl-methadol, $\alpha$ - 1 - acetyl - methadol or $\beta$ - 1 - acetyl-methadol.	60
5	Example 5	Naloxone Hydrochloride	0.5 gram	
		Methadone Hydrochloride	5.0 gram	
		Lactose qs. ad.	100 capsules	
10	Example 6	Naloxone Hydrochloride	0.4 gram	
		Codine Sulfate	30 grams	
		Magnesium Stearate qs.		
		Corn Starch qs. ad.	1000 tablets	
15	Example 7	Naloxone (or a salt thereof)	.050 gram	
		Comphorated Opium Tincture,		
		U.S.P., qs. ad.	100 ml.	
20	Example 8	Naloxone Hydrobromide	1.0 gram	
		Leverphanol	6.0 gram	
		Lactose qs. ad.	1000 capsules	
25	Example 9	Naloxone Hydrobromide	0.10 gram	
		Profadol	2.0 gram	
		Lactose qs. ad.	100 capsules	
30	Example 10	Naloxone Hydrochloride	1.0 gram	
		( $-$ ) $\beta$ -2'-hydroxy-2,9-dimethyl-5-phenyl-6,7-benzomorphan		
		Lactose qs. ad.	1000 capsules	
35	Example 11	Naloxone	0.10 gram	
		( $-$ ) $\alpha$ -5,9-diethyl-2'-hydroxy-2-methyl-6,7-benzomorphan		
		Lactose qs. ad.	100 capsules	
40	Example 12	Naloxone Hydrochloride	0.1 gram	
		Oxymorphone HCl	1.0 gram	
		Lactose qs. ad.	100 capsules	
45	WHAT WE CLAIM IS:-			
	1. An analgesic composition in oral dosage form, which composition comprises an orally active, strong analgesic and an amount of naloxone sufficient to negate the analgesic and/or euphoric action of the composition upon parenteral administration but insufficient to negate the analgesic and/or euphoric action of the composition upon oral administration.			
50	2. A composition as claimed in claim 1, wherein the analgesic is meperidine, oxymorphone, alphaprodine, amilcridine, dextromoramide, dextropropoxyphene, methadone,			
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				115
				120

- oxime, 5 to 50 parts of  $(-\beta - 2'$  - hydroxy - 2,9 - dimethyl - 5 - phenyl - 5,7 - benzomorphan, 13 to 130 parts of  $(-\gamma - 2'$  - hydroxy - 2 - (3 - methyl - 2 - butenyl) - 9 - methyl - 5 - phenyl - 6,7 - benzomorphan, 3 to 50 parts of piriniramide, 5 to 50 parts of  $(-\alpha - 5,9 - diethyl - 2'$  - hydroxy - 2 - methyl - 6,7 - benzomorphan, 5 to 50 parts of ethyl 1 - (2 - dimethylaminoethyl) - 4,5,6,7 - tetrahydro - 3 - methyl - 4 - oxo - 2 - phenylindole - 2 - carboxylate, 20 to 200 parts of 1 - benzoylmethyl - 2,3 - dimethyl - 3 - (m - hydroxyphenyl) - piperidine, 0.1 to 1 parts of N - allyl - 7a - (R) - 2' - hydroxy - 1 - methylbutyl - 6,14 - endoethenotetrahydronorbornane, 24 to 140 parts of  $(-\gamma - 2'$  - hydroxy - 2 - methyl - 6,7 - benzomorphan, 5 to 50 parts of noracetylmethadol, 2 to 20 parts of phenoperidine, 2.5 to 25 parts of  $\alpha - dl$  - methadol, 40 to 400 parts of  $\beta - dl$  - methadol, 0.3 to 3 parts of  $\alpha - l$  - methadol, 0.8 to 8 parts of  $\beta - dl$  - acetylmethadol, 0.8 to 8 parts of  $\beta - l$  - acetylmethadol or 0.4 to 4 parts of  $\beta - 1$  - acetylmethadol.
25. A composition as claimed in claim 1 which comprises 1 mg. or naloxone to 2 to 8 mg. of phenacetine.
26. A composition as claimed in claim 1 which comprises 1 mg. of naloxone to 5 to 10 mg. of methadone.
27. A composition as claimed in claim 1 which comprises 5 mg. of naloxone to 25 to 50 mg. of methadone.
28. A composition as claimed in claim 1 which comprises 1 mg. of naloxone to 30 to 65 mg. of dextropropoxyphene.
29. A composition as claimed in claim 1 which comprises 1 mg. of naloxone to 2 to 8 mg. of levorphanol.
30. A composition as claimed in claim 1 which comprises 1 mg. naloxone to 10 to 40 mg. of profadol.
31. A composition as claimed in claim 1 which comprises 1 mg. of naloxone to 5 to 25 mg. of  $(-\beta - 2'$  - hydroxy - 2,9 - dimethyl - 5 - phenyl - 6,7 - benzomorphan).
32. A composition as claimed in claim 1 which comprises 1 mg. of naloxone to 5 to 25 mg. of  $(-\gamma - 2'$  - hydroxy - 2 - (3 - methyl - 2 - butenyl) - 9 - methyl - 5 - phenyl - 6,7 - benzomorphan, 13 to 130 parts of piriniramide, 5 to 50 parts of  $(-\alpha - 5,9 - diethyl - 2'$  - hydroxy - 2 - methyl - 6,7 - benzomorphan, 5 to 50 parts of ethyl 1 - (2 - dimethylaminoethyl) - 4,5,6,7 - tetrahydro - 3 - methyl - 4 - oxo - 2 - phenylindole - 2 - carboxylate, 20 to 200 parts of 1 - benzoylmethyl - 2,3 - dimethyl - 3 - (m - hydroxyphenyl) - piperidine, 0.1 to 1 parts of N - allyl - 7a - (R) - 2' - hydroxy - 1 - methylbutyl - 6,14 - endoethenotetrahydronorbornane, 24 to 140 parts of  $(-\gamma - 2'$  - hydroxy - 2 - methyl - 6,7 - benzomorphan, 5 to 50 parts of noracetylmethadol, 2 to 20 parts of phenoperidine, 2.5 to 25 parts of  $\alpha - dl$  - methadol, 40 to 400 parts of  $\beta - dl$  - methadol, 0.3 to 3 parts of  $\alpha - l$  - methadol, 0.8 to 8 parts of  $\beta - dl$  - acetylmethadol, 0.8 to 8 parts of  $\beta - l$  - acetylmethadol or 0.4 to 4 parts of  $\beta - 1$  - acetylmethadol.
33. A composition as claimed in claim 1 which comprises 1 mg. or naloxone to 2 to 8 mg. of phenacetine.
34. A composition as claimed in claim 1 which comprises 1 mg. of naloxone to 5 to 10 mg. of methadone.
35. A composition as claimed in claim 1 which comprises 5 mg. of naloxone to 25 to 50 mg. of methadone.
36. A composition as claimed in claim 1 which comprises 1 mg. of naloxone to 30 to 65 mg. of dextropropoxyphene.
37. A composition as claimed in claim 1 which comprises 1 mg. of naloxone to 2 to 8 mg. of levorphanol.
38. A composition as claimed in claim 1 which comprises 1 mg. of naloxone to 10 to 40 mg. of profadol.
39. A composition as claimed in claim 1 which comprises 1 mg. of naloxone to 5 to 25 mg. of  $(-\beta - 2'$  - hydroxy - 2,9 - dimethyl - 5 - phenyl - 6,7 - benzomorphan).
40. A composition as claimed in claim 1 which comprises 1 mg. of naloxone to 5 to 25 mg. of  $(-\gamma - 2'$  - hydroxy - 2 - (3 - methyl - 2 - butenyl) - 9 - methyl - 5 - phenyl - 6,7 - benzomorphan, 13 to 130 parts of piriniramide, 5 to 50 parts of  $(-\alpha - 5,9 - diethyl - 2'$  - hydroxy - 2 - methyl - 6,7 - benzomorphan, 5 to 50 parts of ethyl 1 - (2 - dimethylaminoethyl) - 4,5,6,7 - tetrahydro - 3 - methyl - 4 - oxo - 2 - phenylindole - 2 - carboxylate, 20 to 200 parts of 1 - benzoylmethyl - 2,3 - dimethyl - 3 - (m - hydroxyphenyl) - piperidine, 0.1 to 1 parts of N - allyl - 7a - (R) - 2' - hydroxy - 1 - methylbutyl - 6,14 - endoethenotetrahydronorbornane, 24 to 140 parts of  $(-\gamma - 2'$  - hydroxy - 2 - methyl - 6,7 - benzomorphan, 5 to 50 parts of noracetylmethadol, 2 to 20 parts of phenoperidine, 2.5 to 25 parts of  $\alpha - dl$  - methadol, 40 to 400 parts of  $\beta - dl$  - methadol, 0.3 to 3 parts of  $\alpha - l$  - methadol, 0.8 to 8 parts of  $\beta - dl$  - acetylmethadol, 0.8 to 8 parts of  $\beta - l$  - acetylmethadol or 0.4 to 4 parts of  $\beta - 1$  - acetylmethadol.
41. A composition as claimed in claim 1 which comprises 1 mg. or naloxone to 2 to 8 mg. of phenacetine.
42. A composition as claimed in claim 1 which comprises 1 mg. of naloxone to 5 to 10 mg. of methadone.
43. A composition as claimed in claim 1 which comprises 5 mg. of naloxone to 25 to 50 mg. of methadone.
44. A composition as claimed in claim 1 which comprises 1 mg. of naloxone to 30 to 65 mg. of dextropropoxyphene.
45. A composition as claimed in claim 1 which comprises 1 mg. of naloxone to 2 to 8 mg. of levorphanol.
46. A composition as claimed in claim 1 which comprises 1 mg. of naloxone to 10 to 40 mg. of profadol.
47. A composition as claimed in claim 1 which comprises 1 mg. of naloxone to 5 to 25 mg. of  $(-\beta - 2'$  - hydroxy - 2,9 - dimethyl - 5 - phenyl - 6,7 - benzomorphan).
48. A composition as claimed in claim 1 which comprises 1 mg. of naloxone to 5 to 25 mg. of  $(-\gamma - 2'$  - hydroxy - 2 - (3 - methyl - 2 - butenyl) - 9 - methyl - 5 - phenyl - 6,7 - benzomorphan, 13 to 130 parts of piriniramide, 5 to 50 parts of  $(-\alpha - 5,9 - diethyl - 2'$  - hydroxy - 2 - methyl - 6,7 - benzomorphan, 5 to 50 parts of ethyl 1 - (2 - dimethylaminoethyl) - 4,5,6,7 - tetrahydro - 3 - methyl - 4 - oxo - 2 - phenylindole - 2 - carboxylate, 20 to 200 parts of 1 - benzoylmethyl - 2,3 - dimethyl - 3 - (m - hydroxyphenyl) - piperidine, 0.1 to 1 parts of N - allyl - 7a - (R) - 2' - hydroxy - 1 - methylbutyl - 6,14 - endoethenotetrahydronorbornane, 24 to 140 parts of  $(-\gamma - 2'$  - hydroxy - 2 - methyl - 6,7 - benzomorphan, 5 to 50 parts of noracetylmethadol, 2 to 20 parts of phenoperidine, 2.5 to 25 parts of  $\alpha - dl$  - methadol, 40 to 400 parts of  $\beta - dl$  - methadol, 0.3 to 3 parts of  $\alpha - l$  - methadol, 0.8 to 8 parts of  $\beta - dl$  - acetylmethadol, 0.8 to 8 parts of  $\beta - l$  - acetylmethadol or 0.4 to 4 parts of  $\beta - 1$  - acetylmethadol.
49. A composition as claimed in claim 1 which comprises 1 mg. or naloxone to 2 to 8 mg. of phenacetine.
50. A composition as claimed in claim 1 which comprises 1 mg. of naloxone to 5 to 10 mg. of methadone.
51. A composition as claimed in claim 1 which comprises 5 mg. of naloxone to 25 to 50 mg. of methadone.
52. A composition as claimed in claim 1 which comprises 1 mg. of naloxone to 30 to 65 mg. of dextropropoxyphene.
53. A composition as claimed in claim 1 which comprises 1 mg. of naloxone to 2 to 8 mg. of levorphanol.
54. A composition as claimed in claim 1 which comprises 1 mg. of naloxone to 10 to 40 mg. of profadol.
55. A composition as claimed in claim 1 which comprises 1 mg. of naloxone to 5 to 25 mg. of  $(-\beta - 2'$  - hydroxy - 2,9 - dimethyl - 5 - phenyl - 6,7 - benzomorphan).
56. A composition as claimed in claim 1 which comprises 1 mg. of naloxone to 5 to 25 mg. of  $(-\gamma - 2'$  - hydroxy - 2 - (3 - methyl - 2 - butenyl) - 9 - methyl - 5 - phenyl - 6,7 - benzomorphan, 13 to 130 parts of piriniramide, 5 to 50 parts of  $(-\alpha - 5,9 - diethyl - 2'$  - hydroxy - 2 - methyl - 6,7 - benzomorphan, 5 to 50 parts of ethyl 1 - (2 - dimethylaminoethyl) - 4,5,6,7 - tetrahydro - 3 - methyl - 4 - oxo - 2 - phenylindole - 2 - carboxylate, 20 to 200 parts of 1 - benzoylmethyl - 2,3 - dimethyl - 3 - (m - hydroxyphenyl) - piperidine, 0.1 to 1 parts of N - allyl - 7a - (R) - 2' - hydroxy - 1 - methylbutyl - 6,14 - endoethenotetrahydronorbornane, 24 to 140 parts of  $(-\gamma - 2'$  - hydroxy - 2 - methyl - 6,7 - benzomorphan, 5 to 50 parts of noracetylmethadol, 2 to 20 parts of phenoperidine, 2.5 to 25 parts of  $\alpha - dl$  - methadol, 40 to 400 parts of  $\beta - dl$  - methadol, 0.3 to 3 parts of  $\alpha - l$  - methadol, 0.8 to 8 parts of  $\beta - dl$  - acetylmethadol, 0.8 to 8 parts of  $\beta - l$  - acetylmethadol or 0.4 to 4 parts of  $\beta - 1$  - acetylmethadol.
57. A composition as claimed in claim 1 which comprises 1 mg. or naloxone to 2 to 8 mg. of phenacetine.
58. A composition as claimed in claim 1 which comprises 1 mg. of naloxone to 5 to 10 mg. of methadone.
59. A composition as claimed in claim 1 which comprises 5 mg. of naloxone to 25 to 50 mg. of methadone.
60. A composition as claimed in claim 1 which comprises 1 mg. of naloxone to 30 to 65 mg. of dextropropoxyphene.
61. A composition as claimed in claim 1 which comprises 1 mg. of naloxone to 2 to 8 mg. of levorphanol.
62. A composition as claimed in claim 1 which comprises 1 mg. of naloxone to 10 to 40 mg. of profadol.
63. A composition as claimed in claim 1 which comprises 1 mg. of naloxone to 5 to 25 mg. of  $(-\beta - 2'$  - hydroxy - 2,9 - dimethyl - 5 - phenyl - 6,7 - benzomorphan).
64. A composition as claimed in claim 1 which comprises 1 mg. of naloxone to 5 to 25 mg. of  $(-\gamma - 2'$  - hydroxy - 2 - (3 - methyl - 2 - butenyl) - 9 - methyl - 5 - phenyl - 6,7 - benzomorphan, 13 to 130 parts of piriniramide, 5 to 50 parts of  $(-\alpha - 5,9 - diethyl - 2'$  - hydroxy - 2 - methyl - 6,7 - benzomorphan, 5 to 50 parts of ethyl 1 - (2 - dimethylaminoethyl) - 4,5,6,7 - tetrahydro - 3 - methyl - 4 - oxo - 2 - phenylindole - 2 - carboxylate, 20 to 200 parts of 1 - benzoylmethyl - 2,3 - dimethyl - 3 - (m - hydroxyphenyl) - piperidine, 0.1 to 1 parts of N - allyl - 7a - (R) - 2' - hydroxy - 1 - methylbutyl - 6,14 - endoethenotetrahydronorbornane, 24 to 140 parts of  $(-\gamma - 2'$  - hydroxy - 2 - methyl - 6,7 - benzomorphan, 5 to 50 parts of noracetylmethadol, 2 to 20 parts of phenoperidine, 2.5 to 25 parts of  $\alpha - dl$  - methadol, 40 to 400 parts of  $\beta - dl$  - methadol, 0.3 to 3 parts of  $\alpha - l$  - methadol, 0.8 to 8 parts of  $\beta - dl$  - acetylmethadol, 0.8 to 8 parts of  $\beta - l$  - acetylmethadol or 0.4 to 4 parts of  $\beta - 1$  - acetylmethadol.
65. A composition as claimed in any one of the preceding claims which also includes aspirin, phenacetin, caffeine, acetaminophen, an antihistamine, homatropine methylbromide, phenyltoloxamine citrate, a barbiturate or a mixture thereof.
66. A composition as claimed in any one of Examples 1 to 7.
67. A composition as claimed in any one of Examples 8 to 12.
68. A method of producing a composition as claimed in any one of the preceding claims, which method comprises mixing an orally ineffective, but parenterally effective dose of naloxone with an analgesic dose of an orally active strong analgesic.
69. A method of preventing drug abuse by parenteral administration of an orally active strong analgesic, which method comprises combining the analgesic with naloxone to form a composition as claimed in any one of claims 1 to 18.
70. A method of producing analgesia in non-human mammals, which method comprises orally administering to the mammal a composition as claimed in any one of claims 1 to 18.

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